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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/856,907 | 05/29/2001 | Andrew Raymon Morton Bradbury | 6278 | 6402 |
| <div>7590 12/12/2007</div> <div>Samuels Gauthier & Stevens Suite 3300 225 Franklin Street Boston, MA 02110</div> <div>EXAMINER LUNDGREN, JEFFREY S</div> <div>ART UNIT 1639 PAPER NUMBER</div> <div>MAIL DATE 12/12/2007 DELIVERY MODE PAPER</div> | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

| | | | |
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| <p align="center">Office Action Summary</p> | <p>Application No.</p> <p>09/856,907</p> | <p>Applicant(s)</p> <p>BRADBURY ET AL.</p> | |
| | <p>Examiner</p> <p>Jeff Lundgren</p> | <p>Art Unit</p> <p>1639</p> | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 September 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-92 is/are pending in the application.
- 4a) Of the above claim(s) 3 and 49-92 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 4-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| <p>1) <input type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application</p> <p>6) <input type="checkbox"/> Other: _____.</p> |
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DETAILED ACTION

Status of the Claims

Claims 1-92 are pending in the instant Office Action; claims 3 and 49-92 are withdrawn as being directed to a non-elected invention; claims 1, 2 and 4-48 are the subject of the Office Action below.

Claim Objections and Rejections – Withdrawn

Any objection to the claims or rejection of the claims that is not reiterated in the instant Office Action is considered withdrawn.

Claim Rejections - 35 USC § 102—Maintained

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 1, 2 and 4-48 as anticipated by Johnson:

The rejection of claims 1, 2 and 4-48, under 35 U.S.C. § 102(b) as being anticipated by Johnson et al., U.S. Patent No. 5,733,743, issued March 31, 1998, is maintained.

Applicants traverse the rejection and allege that Johnson is not related to the claimed invention because Johnson is directed to a “two-vector” system, whereas the claimed invention is directed to a “single vector” (Reply, page 14, last two paragraphs). Applicants quote certain excerpts of Johnson, and point to Figure 2, and drawn the conclusion that Johnson does not disclose a single vector system (page 15). Applicants reiterate a portion of their disclosure that allegedly provides certain contrast with the related art (pages 15 and 16).

Applicants further assert that their invention solves a technical problem with the art, namely that the art relies on using different origins of replication because of problems that are

generally known as "origin interference" (page 16). Applicants next points out that Johnson discloses using phage and phagemid vectors.

Applicants arguments have been considered in full, however are unpersuasive.

While it is true that Johnson does teach the combination of two vectors to produce a product vector, and in certain instances uses different origins of replication, Applicants claims clearly read on Johnson.

Johnson clearly teaches introducing at least two members of an initial population, wherein the initial population could be, for example, the vectors shown in Figure 3. In Figure 3, Johnson teaches two vector *each having* the same *origins* of replication, *i.e.*, "ori" and/or "M13 ori" represented by the open-oval and the filled-triangle. Regardless of the fact that the source of the coding sequences are phage and phagemid does remove Johnson as prior art because there is nothing in the claim that states otherwise.

Applicants' currently claimed invention does not distinguish over the art. Instead, Applicants suggest that their invention overcomes a well-known phenomenon in the art that relates to interference from using different constructs sharing a single origin. Applicants arguments appear to imply that their invention finds success in utilizing a vector library where all the different members have only a single origin of replication. This clearly is not what is claimed - the claims are open to additional origins of replication, such as members having two origins of replication. In fact, this is what is clearly shown in Applicants' Figure 1, wherein the origins Ff and ColeE1 are used in each vector.

Reiterated Rejection:

Claim 1 is directed to a method of preparing a nucleic acid library, said method comprising introducing at least two members of an initial population of nucleic acid molecules into at least one cell, said population of nucleic acid molecules comprising two or more individual nucleic acids each of which consists of a nucleic acid sequence that is identical for each molecule and that includes an origin of replication; and a nucleic acid sequence that varies between members of said population and which comprises a substrate for recombination, said introducing resulting in recombination of said substrate for recombination between at least two

members of the population thereby producing a population comprising recombined nucleic acid members. Claim 48 is directed to a library of nucleic acids for the purpose of claim.

Johnson teaches methods for the production of members of specific binding pairs (sbp), e.g., antibodies, using display on the surface of secreted replicable genetic display packages (rgdps), e.g., filamentous phage, via certain host cells. To produce a library of great diversity, recombination occurs between first and second vectors comprising nucleic acid encoding first and second polypeptide chains of sbp members respectively, thereby producing recombinant vectors each encoding both a first and a second polypeptide chain component of an sbp member. The recombination may take place in vitro or intracellularly and may be site-specific, e.g. involving use of the loxP sequence and mutants thereof. Recombination may take place after prior screening or selecting for rgdps displaying sbp members which bind complementary sbp member of interest (see Figs. 3A and 3B, and description thereof). As shown in Figs 3A and 3B, both nucleic acid members are introduced to the cell. Accordingly, claims 1 and 48 are anticipated.

As in claims 2 and 4-10, Johnson teaches the use of various recombination mechanisms for creating the library; Johnson states:

“Another way of enriching for productive recombination events is to employ mutant loxP sites. Several mutants of the loxP sequence are known, and these are compromised with respect to their ability to recombine with each other and the wild-type loxP sequence (Hoess, R. H., Wierzbicki, A. and Abremski, K. (1986) Nucl. Acids Res. 14, 2287-2300). For example, loxP 511 has a G→A point mutation in the central 8 bp segment, with the result that it will only recombine with other loxP 511 sites, but not the wild-type loxP sequence (Hoess, R. H., Wierzbicki, A. and Abremski, K. (1986) et supra.). Placement of wild-type and mutant loxP sequence combinations can direct which recombination events are possible: their use is described in example 1. Other mutant loxP sites are known but their abilities to recombine with each other and the wild-type loxP sequence have not been extensively characterised, presumably loxP 511 is not unique. Provision of different mutant loxP sites in the vectors would permit even greater control over the occurrence of recombination events perhaps leading to more complex, controllable and efficient recombination strategies being possible.”

Johnson, paragraph bridging cols. 16 and 17 (emphasis added). Accordingly, claims 11-13 are anticipated.

As in claim 14-23, Johnson teaches a range of reagents for delivering the nucleic acid library members, such as the phage:

“In one embodiment, [t]he recombination is intracellular and takes place in a *bacterial host* which replicates the recombinant vector preferentially over the first vectors and the second vectors. This may be used to enrich selection of successful recombination events. The intracellular recombination may take place in a bacterial host which replicates plasmids preferentially over phages or phagemids, or which replicates phages or phagemids preferentially over plasmids. For instance, the bacterial host may be a PolA strain of *E. coli* or of another gram-negative bacterium. PolA cells are unable to support replication of plasmids, but can support replication of *filamentous phage and phagemids (plasmids containing filamentous phage intergenic regions)*. So, for instance, if the first vectors are plasmids containing a first marker gene, and the second vectors are phage or phagemids containing a second marker gene, selection for both markers will yield recombinant vectors which are the product of a successful recombination event, since recombination transferring the first marker from plasmid must take place in order for that marker to be replicated and expressed.”

Johnson, col. 12, lines 42-61; and previously where Johnson states:

“The particle may be a virus e.g. a bacteriophage such as *fd* or *M13* [i.e., a **Ff family phage member**].”

Johnson, col. 7, lines 59 and 60 (emphasis added). Accordingly, the claim limitation of claim 25, 35, 38 and 43, are met by the aforementioned paragraphs.

The expression cassette limitation of claim 26 is met by Figs. 3A and 3B and the corresponding description (see above). As in claim 27, one or more polypeptides are encoded for; as in claim 28, the encoded polypeptides are flanked by the recombination sites (see Figs. 3A and 3B and the corresponding description). As noted above, the limitations of phage, phagemid and bacterium polypeptide expression in claim 29, 34, 36 and 37, are all taught by Johnson.

As also noted above, the specific binding pair limitations of claim 30 are met by the variable chain (light and heavy) teaching in Johnson, where Johnson teaches the recombined

antibodies (see above), as in claims 31, 39 and 40 (*i.e.*, scFv; Johnson col. 1, lines 52-59; see also Johnson, col. 8, lines 1-7). Regarding claims 32 and 33, Johnson teaches CDR3 and the VH and VL regions of the polypeptide (see Example 1; also see Figs. 3A and 3B and the corresponding description). As in claim 42, Johnson discloses a polypeptide linker comprising a recombination site of the V region (Figs. 3A and 3B and the corresponding description). Regarding claims 44-47, Johnson teaches:

“So, for instance, if the *first vectors are plasmids containing a first marker gene, and the second vectors are phage or phagemids containing a second marker gene*, selection for both markers will yield recombinant vectors which are the product of a successful recombination event, since recombination transferring the first marker from plasmid must take place *in order for that marker to be replicated and expressed.*”

Johnson, col. 12, lines 54-61 (emphasis added).

Accordingly, the rejection is maintained.

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipso verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JSL/


J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER